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(54) Title: ANTIBIOTIC COMPOSITIONS FOR TREATMENT OF THE EYE, EAR AND NOSE

(57) Abstract

Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti–inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues.

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ANTIBIOTIC COMPOSITIONS FOR TREATMENT OF THE EYE, EAR AND NOSE

Background of the Invention

The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class of antibiotics. The compositions of the present invention may also contain one or more anti-inflammatory agents.

The use of quinolone antibiotics to treat infections represents the current state of the art in the field of ophthalmic pharmaceutical compositions and methods of treatment. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN™ (Ciprofloxacin 0.3%) Ophthalmic Solution. The following quinolones have also been utilized in ophthalmic antibiotic compositions:

Quinolone	Product	Manufacturer
Ofloxacin	OCUFLOX™	Allergan
Norfloxacin	CHIBROXIN™	Merck
Lomefloxacin	LOMEFLOX™	Senju

The foregoing quinolone antibiotic compositions are generally effective in treating ophthalmic infections, and have distinct advantages over prior ophthalmic antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which are primarily useful against gram negative pathogens; and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the ophthalmic quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

There is an even greater need for effective topical compositions and methods for treating otic and nasal infections, particularly bacterial infections. The use of oral antibiotics to treat otic infections in children has limited efficacy, and creates a serious risk of pathogen resistance to the orally administered antibiotics.

Ophthalmic, otic and nasal infections are frequently accompanied by inflammation of the infected ophthalmic, otic and nasal tissues and perhaps even surrounding tissues. Similarly, ophthalmic, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for ophthalmic, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

Summary of the Invention

The invention is based on the use of a potent new class of antibiotics to treat ophthalmic, otic and nasal infections, as well as the prophylactic use of these antibiotics following surgery or other trauma to ophthalmic, otic or nasal tissues. The compositions

of the present invention may also be administered to the affected tissues during ophthalmic, otic or nasal surgical procedures to prevent or alleviate post-surgical infections.

The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation asociated with infections of ophthalmic, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to ophthalmic, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to ophthalmic, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis. blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

Examples of otic conditions that may be treated with the compostions of the present invention include otitis externa and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

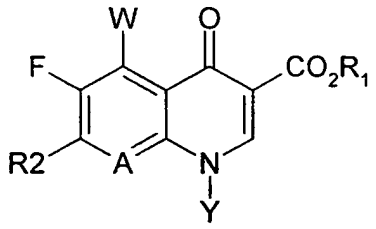
The compositions of the present invention are specially formulated for topical application to ophthalmic, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic, otic and nasal tissues, including tissues that have been

compromised as the result of preexisting disease, trauma, surgery or other physical conditions.

Detailed Description of the Invention

The antibiotics used in the compositions and methods of the present invention have the following formula:

(I)



wherein

R1 is hydrogen, a pharmaceutically acceptable cation, or (C1 -C6) alkyl;

Y, when taken independently, is ethyl, t-butyl, vinyl, cyclopropyl, 2-fluoroethyl, p-fluorophenyl, or o,p-difluorophenyl;

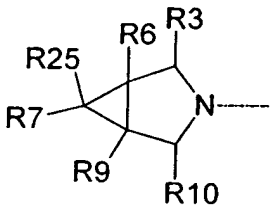
W is hydrogen, F, Cl, Br, C1 -C4 alkyl, C1 -C4 alkoxy, NH2 or NHCH3;

A is CH, CF, CCl, COCH3, C-CH3, C-CN or N; or

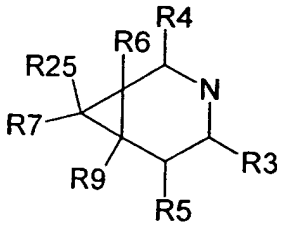
A is carbon and is taken together with Y and the carbon and nitrogen to which A and Y are attached to form a five or six membered ring which may contain oxygen or a double bond, and which may have attached thereto R8 which is methyl or methylene;

and

R2 is



or

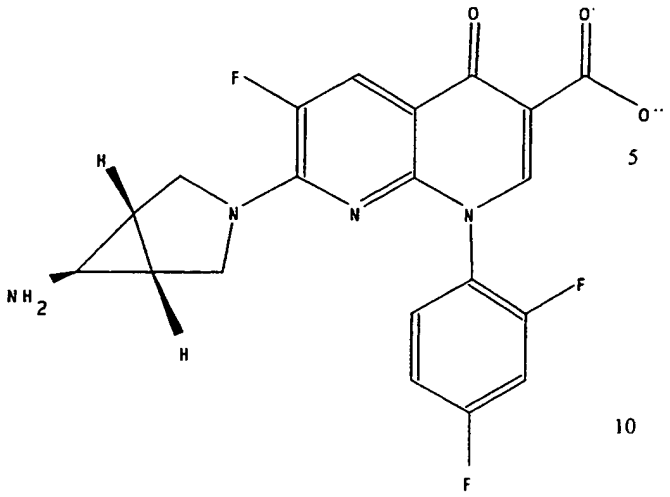


wherein:

R3, R4, R5, R6, R7, R9, R10 and R25 are each independently H, CH3, CH2NH2, CH2NHCH3 or CH2NHC2H5, and R5, R6, R7, and R9 may also independently be NH2, NHCH3 or NHC2H5, provided that not more than three of R3, R4, R5, R6, R7, R9, R10 and R25 are other than hydrogen, and if three of these substituents are not hydrogen, at least one of them is methyl.

The antibiotics utilized in the present invention also include prodrugs of the compounds of formula (I) having a free amino group, as well as pharmaceutically useful hydrates and salts of the compounds of formula (I).

The compound Trovafloxacin is most preferred. Trovafloxacin has the following structure:



Further details regarding the structure, preparation, and physical properties of Trovafloxacin and other compounds of formula (I) are provided in U.S. Patent No. 5,164,402.

The concentrations of the antibiotics of formula (I) in the compositions of the present invention will vary depending on the intended use of the compositions (e.g., treatment of existing infections or prevention of post-surgical infections), and the relative antimicrobial activity of the specific antibiotic selected. The antimicrobial activity of antibiotics is generally expressed as the minimum concentration required to inhibit the growth of a specified pathogen. This concentration is also referred to as the "minimum inhibitory concentration" or "MIC". The term "MIC90" refers to the minimum concentration of antibiotic required to inhibit the growth of ninety percent (90%) of the strains of a species. The concentration of an antibiotic required to totally kill a specified bacteria is referred to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Trovafloxacin for several bacteria commonly associated with ophthalmic, otic and nasal infections are provided in the following table:

Microorganism	MIC_{90}
S. aureus/methicillin sensitive	0.03
S. aureus/methicillin resistant	2.0
S. aureus/quinolone resistant	4.0
S. epidermidis/methicillin sensitive	0.06
S. epidermidis/methicillin resistant	4.0
S. pneumoniae/penicillin sensitive	0.25
S. pneumoniae/penicillin resistant	0.25
P. aeruginosa	2.0
H. influenzae/β-lactamase positive	0.03
H influenzae/βlactamase negative	0.03

All of the foregoing concentrations are expressed as micrograms per milliliter ("mcg/ml").

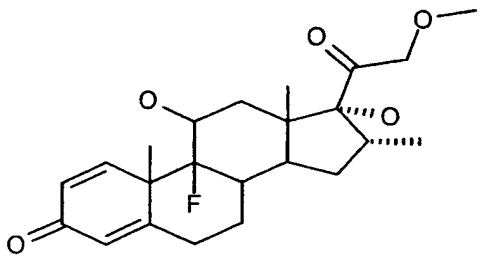
The appropriate antibiotic concentration for ophthalmic compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the infected tissues equal to or greater than the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with otic or nasal infections. Such amounts are referred to herein as "an antimicrobial effective amount". The compositions of the present invention will typically contain one or more compounds of formula (I) in a concentration of from about 0.1 to about 1.0 percent by weight ("wt. %") of the compositions.

The compositions of the present invention may also contain one or more anti-inflammatory agents. The anti-inflammatory agents utilized in the present invention are

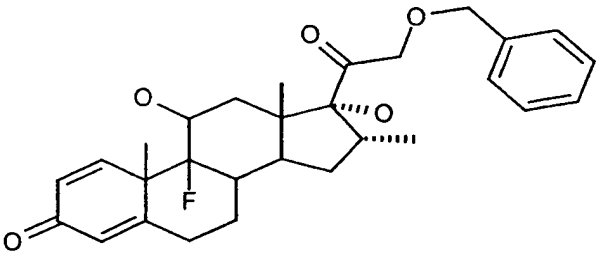
broadly classified as steroidal or non-steroidal. The preferred steroidal anti-inflammatory agents are glucocorticoids.

The preferred glucocorticoids for ophthalmic and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

The dexamethasone derivatives described in U.S. Patent No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to compositions for treating ophthalmic inflammation. The following compounds are especially preferred:



AL-1529



AL-2512

These compounds are referred to herein as "21- ether derivatives of dexamethasone". The 21-benzyl ether derivative (i.e., compound AL-2512) is particularly preferred.

The preferred non-steroidal anti-inflammatory agents are: prostaglandin H synthetase inhibitors (Cox I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac,

indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusinal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib, P54, etodolac, L-804600 and S-33516; PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFkB transcription factor; or other anti-inflammatory agents known to those skilled in the art.

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted ophthalmic, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein as "an anti-inflammatory effective amount". The compositions of the present invention will typically contain one or more anti-inflammatory agents in an amount of from about 0.01 to about 1.0 wt.%.

The compositions are typically administered to the affected ophthalmic, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable amount of an ointment, gel or other solid or semisolid composition, one to four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected ophthalmic, otic or nasal tissues during surgical procedures.

The ophthalmic, otic, and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one or more anti-inflammatory

agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The ophthalmic compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and ophthalmic tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram of water ("mOsm/kg"), but will preferably be about 300 mOsm/kg.

Ophthalmic, otic, and nasal products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

The use of viscosity enhancing agents to provide the compositions of the invention with viscosities greater than the viscosity of simple aqueous solutions may be desirable to increase absorption of the active compounds by the target tissues or increase the retention time in the eye, ear or nose. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

The following examples are provided to further illustrate the ophthalmic, otic, and nasal compositions of the present invention.

Example 1

Ophthalmic/Otic /Nasal Solution

Ingredient	Amount (wt. %)
Trovafloxacin	0.35
Sodium Acetate	0.03
Acetic Acid	0.04
Mannitol	4.60
EDTA	0.05
Benzalkonium Chloride	0.006
Water	q.s. 100

Example 2

Ophthalmic/Otic/Nasal Suspension

Ingredient	Amount (wt. %)
Trovafloxacin	0.3
Dexamethasone, Micronized USP	0.10
Benzalkonium Chloride	0.01
Edetate Disodium, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or	
Sodium Hydroxide, NF	q.s. for pH adjustment to 5.5
Purified Water, USP	q.s. to 100

Example 3

Ophthalmic Ointment

Ingredient	Amount (wt.%)
Trovafloxacin	0.35
Mineral Oil, USP	2.0
White petrolatium, USP	q.s 100

Example 4

Ophthalmic Ointment

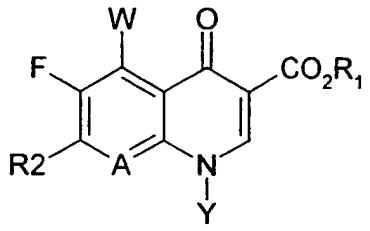
Ingredient	Amount (wt.%)
Trovafloxacin	0.3
Fluorometholone Acetate, USP	0.1
Chlorobutanol, Anhydrous, NF	0.5
Mineral Oil,USP	5
White Petrolatum, USP	q.s. 100

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

What is claimed is:

1. A topical ophthalmic, otic or nasal pharmaceutical composition comprising an antimicrobial effective amount of one or more compounds of the formula:

(I)



wherein

R1 is hydrogen, a pharmaceutically acceptable cation, or (C1 -C6) alkyl;
Y, when taken independently, is ethyl, t-butyl, vinyl,
cyclopropyl, 2-fluoroethyl, p-fluorophenyl, or o,p-difluorophenyl;

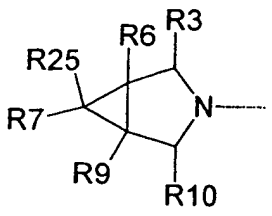
W is hydrogen, F, Cl, Br, C1 -C4 alkyl, C1 -C4 alkoxy, NH2 or NHCH3 ;

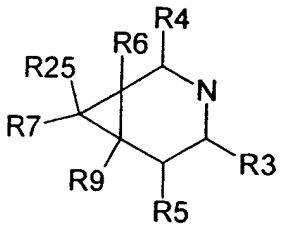
A is CH, CF, CCl, COCH3, C-CH3, C-CN or N; or

A is carbon and is taken together with Y and the carbon and nitrogen to which A and Y are attached to form a five or six membered ring which may contain oxygen or a double bond, and which may have attached thereto R8 which is methyl or methylene;

and

R2 is





or

wherein:

R3, R4, R5, R6, R7, R9, R10 and R25 are each independently H, CH3, CH2NH2, CH2NHCH3 or CH2NHC2H5, and R5, R6, R7, and R9 may also independently be NH2, NHCH3 or NHC2H5, provided that not more than three of R3, R4, R5, R6, R7, R9, R10 and R25 are other than hydrogen, and if three of these substituents are not hydrogen, at least one of them is methyl; or

a prodrug of a compound of formula (I) having a free amino group, or a pharmaceutically useful hydrate or salt of a compound of formula (I); and

a pharmaceutically acceptable vehicle therefor.

2. A topical composition according to Claim 1, wherein the composition further comprises an anti-inflammatory effective amount of a steroidal or non-steroidal anti-inflammatory agent.

3. A topical composition according to Claim 2, wherein the anti-inflammatory agent comprises a glucocorticoid.

4. A topical composition according to Claim 3, wherein the glucocorticoid is selected from the group consisting of dexamethasone, rimexolone, prednisolone, fluorometholone, hydrocortisone, mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

5. A topical composition according to Claim 2, wherein the anti-inflammatory agent comprises a non-steroidal agent selected from the group consisting of prostaglandin H synthetase inhibitors, PAF antagonists, and PDE IV inhibitors.

6. A topical composition according to Claim 1, wherein the compound of formula (I) comprises trovafloxacin.

7. A topical composition according to Claim 6, wherein the composition further comprises an anti-inflammatory effective amount of a steroidal or non-steroidal anti-inflammatory agent.

8. A method of treating or preventing ophthalmic, otic or nasal infections, which comprises topically applying a therapeutically effective amount of the composition of Claim 1 to the affected ophthalmic, otic or nasal tissue.

9. A method of treating or preventing ophthalmic, otic or nasal infections and attendant inflammation, which comprises topically applying a therapeutically effective amount of the composition of Claim 2 to the affected ophthalmic, otic or nasal tissue.

10. A method of treating or preventing ophthalmic, otic or nasal infections and attendant inflammation, which comprises topically applying a therapeutically effective amount of the composition of Claim 7 to the affected ophthalmic, otic or nasal tissue.

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/US 99/22624

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/435 A61K45/06 A61K31/57 A61P27/02 , A61P27/16
//(A61K31/57,31:44),(A61K31/57,31:435)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	EP 0 982 031 A (PFIZER LTD ;PFIZER (US)) 1 March 2000 (2000-03-01) column 4, line 56 -column 5, line 10 column 5, line 30-46; claims	1,6,8
P,X	MCLEOD, S. D. (1) ET AL: "The effect of topical trovafloxacin in a rabbit streptococcus pneumoniae keratitis model." IOVS, (MARCH 15, 1999) VOL. 40, NO. 4, PP. S689. MEETING INFO.: ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY FORT LAUDERDALE, FLORIDA, USA MAY 9-14, 1999 ASSOCIATION FOR RESEARCH IN VISION AND OPTHALMOLOGY., XP000892625 the whole document	1,6,8

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[X] Further documents are listed in the continuation of box C.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2000	05/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Veronese, A

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 06435 A (UNIV VANDERBILT ;MITCHELL WILLIAM M (US); STRATTON CHARLES W (US)) 19 February 1998 (1998-02-19) * See page 31, table 3 "Trovafloxacin" * page 41, line 1 page 41, line 12,13 page 43, line 18-22	1,6
Y	US 5 164 402 A (BRIGHTY KATHERINE E) 17 November 1992 (1992-11-17) cited in the application the whole document	1-10
Y	WO 90 01933 A (ALCON LAB INC) 8 March 1990 (1990-03-08) the whole document	1-10
Y	WO 96 39146 A (BAYER AG) 12 December 1996 (1996-12-12) the whole document	1-10
Y	J VINCENT ET AL: "Pharmacokinetics and safety of trovafloxacin in healthy male volunteers following administration of single intravenous doses of the prodrug, alatrofloxacin" JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY,GB,SAUNDERS CO. LTD., LONDON, vol. 39, no. SUPPL. B, 1 January 1997 (1997-01-01), pages 75-80, XP002083830 ISSN: 0305-7453 the whole document	1-10
P,X	US 5 912 255 A (BUSSELL LETANTIA) 15 June 1999 (1999-06-15) the whole document	1,6,8
A	US 5 223 493 A (BOLTRALIK JOHN J) 29 June 1993 (1993-06-29) cited in the application the whole document	1-10
P,Y	KAW, P. (1) ET AL: "The penetration of trovafloxacin into the eye and CSF of rabbits." IOVS, (MARCH 15, 1999) VOL. 40, NO. 4, PP. S88. MEETING INFO.: ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY FORT LAUDERDALE, FLORIDA, USA MAY 9-14, 1999 ASSOCIATION FOR RESEARCH IN VISION AND OPTHALMOLOGY., XP000892619 the whole document	1,6,8

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Inter... onal Application No
PCT/US 99/22624

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NG E W ET AL: "Treatment of experimental Staphylococcus epidermidis endophthalmitis with oral trovafloxacin." AMERICAN JOURNAL OF OPHTHALMOLOGY, (1998 AUG) 126 (2) 278-87. , XP000892627 the whole document	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 22624

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/22624

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